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Law and Patent Offices

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Prague, April 22, 2005

International Bureau of WIPO
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Re: International application No. PCT/CZ2004/000053
Comments on the Written opinion of the International Searching Authority

Your ref.: PCT/CZ2004/000053
Our ref.: 150382/KB

Responsive to the Written Opinion of the International Searching Authority as mailed on February 25, 2005 we present, in due time, our attitude to the matter comprised in the Written Opinion.

By the Written opinion the International Searching Authority reproaches to the inventions disclosed in claims 1 to 5 the absence of the inventive step in sense of Article 33(3) PCT which ISA´s standpoint is justified by the reasoning as comes after"

The present problem to be solved is the provision of an oxaliplatin lyophilizate which is stable and which has an alcoholic sugar of non-animal origin as a carrier. The document D1 [WO 94/12193 A (Debiopharm S.A.; June 9, 1994)] is regarded as being the closest prior art to the subject-matter of claim 1 and 4, and discloses a composition of oxaliplatin lyophilizate in combination with an alcoholic sugar of non-animal origin such as a carrier (see in particular claim 7, examples and p. 4, 3rd § in D1). The subject-matter of claim 1 therefore differs from this known oxaliplatin lyophilizate in that the weight

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ratio of oxaplatin to the alcoholic sugar of non-animal origin is 1:3 to 1:17. However, the selected weight ratio does not seem to contribute to establish inventive step over D1, since no evidence over the importance of the selected weight ration for stabilizing characteristics of the composition is derivable from the present application. Thus, the solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT). The same reasoning applies, mutatis mutandis, to the subject matter of the corresponding independent claim 4, which therefore is also considered not inventive.

First of all, it is worth noting that D1 does not at all occupy with solving the problem of a risk of viral contamination of pharmaceutical compositions comprising lactose as a carrier which is, on the contrary, the principal concern of the solution of the present application. The most weighty fact testifying for this is that claim 7 recommends, as an preferred embodiment of the pharmaceutical composition according to D1, a use of lactose as carrier regardless of that it is very lactose that is an optional cause of the viral contamination. Nowhere in D1 at all a risk of viral contamination is either commonly mentioned or put into a relation with lactose. Nowhere in D1 at all either a mention or a mere hint concerning that the risk of the viral contamination could be eliminated by using specifically an alcoholic sugar of non-animal origin replacing lactose in function of carrier is made. In addition to it, D1 mentions lactose, glucose, mannitol and sorbitol, that are by the way habitually usable carriers, as equally effective without making amongst them any difference which, in turn, means that all these carriers are according to the spirit of D1 preferred in the same way.
As distinct from the present application, D1 solves the problem of a simultaneous administration of cisplatin and oxaliplatin in a single aqueous solution by discovering such composition of the lyophilizate of the pharmaceutical composition comprising both cisplatin and oxaliplatin that

prevents oxaliplatin from precipitating after an administerable aqueous solution is reconstituted from said lyophilizate. It is hence evident that the problem having been solved by D1 is quite different from that having been solved by the present application.

Nevertheless, let´s admit that the person skilled in the art working towards removing the risk of the viral contamination optionally caused by lactose in the composition comprising oxaliplatin as an active ingredient would have taken, from D1, the knowledge of that the problematic (in terms of viral contamination) lactose can be replaced with a non-problematic (in terms of viral contamination, as well) alcoholic sugar of non-animal origin (mannitol or sorbitol of D1) and that this person would have implemented the lyophilization, in the same way as usually carried out in the presence of lactose, of an aqueous solution containing the alcoholic sugar instead of lactose. Then it is evident that the obtained absolutely unsatisfactory result of such a lyophilization (see the third complete paragraph of page 3 of the present application: " During workup of solutions in which lactose is simply replaced with mannitol, the lyophilizate often escapes from the vials and the glass vials crack as the result of increased mechanical tension due to the changing volume of the frozen solution which is particularly manifested by falling away of the vial bottom during the freeze-drying procedure"), brought about by that the alcoholic sugars do not exhibit such excellent cryoprotective properties as lactose does, would have surely taught the person skilled in the art from persisting in substituting the alcoholic sugar for lactose. If the person skilled in the art had wanted all the same to realize said substitution of the alcoholic sugar of non-animal origin for lactose in order to reach the beneficial anti-viral contamination effect of the alcoholic sugar this person would have been faced with a problem the solution of which was not obvious from D1. The thing is, D1 is perfectly silent on the above described lyophilization problems and mentions the implementation of the lyophilization only in a slovenly fashion (lines 8-11 of p.5 of D1: "The acid aqueous solution is then lyophilized

using conventional technical means in the container in which the drug reconstitution is finally carried out"; ex. 1 of D1: "...The buffered acid mixture after having been sterile filtered is poured to a sterile container and frozen to -55°C. After a far-reaching lyophilization implemented in a suitable apparatus the obtained product was subjected to..."; ex. 3 of D1: "then the lyophilization is implemented by freezing to a temperature of from -50°C to -60°C...").

It follows from the present application that the present inventors solved the lyophilization problem connected with the substitution of the alcoholic sugar of non-animal origin for lactose by establishing a very sophisticated time-dependent temperature regime performed under strictly defined concentration and space conditions (see the present claim 4) which very required a considerable degree of the inventiveness and experimental work. Thus it ensues from the foregoing that the substance of the present invention does not consists in a mere substitution of the alcoholic sugar of non-animal origin for lactose but does consist in discovering the specific lyophilization regime that as the single one enables the mentioned substitution to be realized in a non-problematic way. Taking account of this, the solution as comprised in the present claims 1 to 5 should be regarded as including the inventive step and hence satisfying the condition of Article 33(3) PCT.

In behalf of
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